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(54) Title of Invention

Novel Optical Resolving Agent and Production of Optically Active Amines Using That

(57) Abstract

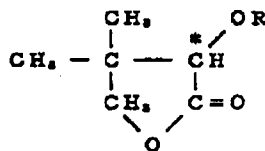
Objective

To provide an effective resolving agent for producing optically active amines by optically resolving (\pm)-amines and also a method for producing optically active amines characterized by

using this resolving agent.

Constitution

Optically active pantolactone, which is produced inexpensively industrially, is converted to an optically active O-alkylpantolactone represented by the general formula

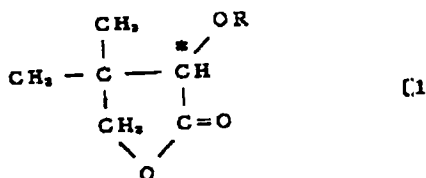


(wherein R indicates a C₁-C₄ lower alkyl group or benzyl group, and * indicates an asymmetric carbon) by a novel method. These compounds are known to be useful for the optical resolution of various (±)-amines. Efficient optical resolution is possible by the combination of, for example, 1-phenylethylamine and O-methylpantolactone, 1-(1-naphthyl)ethylamine and O-ethylpantolactone, 1-methyl-3-phenylpropylamine and O-*n*-propylpantolactone, and 1-phenylpropylamine and O-benzylpantolactone.

CLAIMS

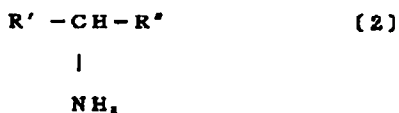
1. O-Alkylpantolactones represented by general formula [1]

[Chemical formula 1]



(wherein R indicates a C₁-C₄ lower alkyl group or benzyl group, and * indicates an asymmetric carbon) as optical resolving agents.

2. A method for producing optically active amines characterized by using an O-alkylpantolactone represented by general formula [1] as the resolving agent when optically resolving an amine represented by general formula [2]



(wherein R' and R'' indicate respectively different lower alkyl groups, phenyl groups which may

have 1-3 lower alkyl, halogen, or alkoxy groups, naphthyl groups, or aralkyl groups).

3. A method for producing optically active amines characterized in that, when optically resolving (\pm)-1-phenylethylamine, (\pm)-1-phenylpropylamine, (\pm)-1-(1-naphthyl)ethylamine, or (\pm)-1-methyl-3-phenylpropylamine, an O-alkylpantolactone represented by general formula [1] is used as the optical resolving agent, two diastereomer salts of this resolving agent and the above-mentioned (\pm)-amines are produced, and the (\pm)-amine is optically resolved by utilizing the difference in degree of solubility between these diastereomer salts.

DETAILED DESCRIPTION OF THE INVENTION

[0001]

Industrial field of use

The present invention relates to a novel method for producing optically active amines.

[0002]

Prior art and its problems

As a method for obtaining optically active amines, optical resolution is very effective and is widely used. However, the optical resolving agents for amines used in the past were expensive or only one optically active form was inexpensive, or recovery was not easy.

[0003]

For example, the L-form of tartaric acid is easily obtained from nature and is inexpensive, but the D-form is expensive. Mandelic acid is inconvenient to recover. Pantolactone, after used as pantoic acid, is lactonized under acidic conditions, so it is easy to recover, but it dissolves in water, so it must be concentrated or the number of extractions with organic solvent must be increased.

[0004]

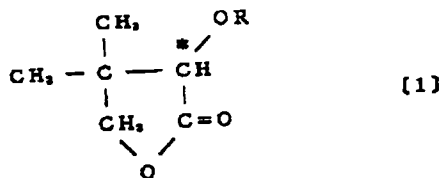
Means of solving the problems

The present inventors focused on the fact that D- and L- optically active pantolactone can be produced inexpensively industrially and investigated whether optical resolution to obtain optically active amines for which the drawbacks indicated above were improved would be possible by deriving these.

[0005-0007]

That is, they thought that by synthesizing O-alkylpantolactones represented by general formula [1]

[Chemical formula 2]



with a lower alkyl group or benzyl group attached to the 2-position hydroxyl group of pantolactone (wherein R indicates a C₁-C₄ lower alkyl or benzyl group, and * indicates an asymmetric carbon), pantolactone could be converted to derivatives more suited to the amines resolved and also lower water solubility and make the compound easier to recover, and industrial optical resolution might be possible.

[0008]

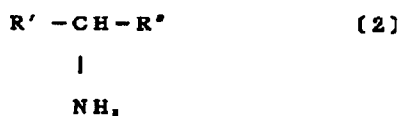
Optically active O-alkylpantolactones [1] can be easily produced by the method that the present inventors have newly developed. That is, they can be produced by reacting optically active pantolactone with an alkyl halide in the presence of a metal oxide.

[0009]

As the alkyl halide, methyl iodide, ethyl iodide, ethyl bromide, *n*-propyl iodide, *n*-propyl bromide, and benzyl bromide can be mentioned. As the metal oxide, silver oxide and barium oxide can be mentioned.

[0010]

The novel optically active O-alkylpantolactones [1] obtained in this manner can be reacted with an amine represented by general formula [2]



(wherein R' and R'' indicate respectively different lower alkyl groups, phenyl groups which may have 1-3 lower alkyl, halogen, or alkoxy groups, naphthyl groups, or aralkyl groups) to produce two diastereomers, and optical resolution can be carried out by utilizing the difference in degree of solubility of these salts in solvents.

[0011]

The optical resolution method of this invention will now be described concretely. An optically active O-alkylpantolactone [1] and (\pm)-amine (2) are heated and reacted in water, or an optically active O-alkylpantolactone [1] is heated in an aqueous alkali solution to open the lactone ring, and a hydrochloride solution of (\pm)-amine is added to that and reacted. After the reaction has concluded, the reaction product is crystallized by cooling, or after concentration, a suitable organic solvent is added and this is heated and dissolved, and then, if necessary, inorganic salts such as NaCl are removed by filtration, and the filtrate is cooled, or if necessary, concentrated, thereby selectively crystallizing an amine salt of difficultly soluble O-alkylpantoic acid, and solid-liquid separation is carried out.

[0012]

The amount of (\pm)-amine [2] used is 0.4-1.2 moles, more preferably 0.9-1.1 moles, per mole of optically active O-alkylpantolactone [1].

[0013]

If the optically active salt obtained in this manner is still not optically pure, a pure salt can be easily obtained by recrystallization as necessary. The desired optically active amine can be obtained by adding an alkali to the salt obtained to decompose it and then extracting with an organic solvent. The aqueous layer is acidified with hydrochloric acid or the like and then lactonized by heating, and an optically active O-alkylpantolactone [1] can be easily and efficiently recovered by extracting with an organic solvent. Or, the desired optically active amine can be easily obtained by adding hydrochloric acid to the salt obtained to decompose it, lactonizing by heating, extracting with an organic solvent, recovering the optically active O-alkylpantolactone [1], and then alkalizing the aqueous layer and extracting with an organic solvent.

[0014]

As examples of the amines [2] that can be optically resolved, 1-phenylethylamine, 1-phenylpropylamine, 1-(1-naphthyl)ethylamine, and 1-methyl-3-phenylpropylamine can be mentioned.

[0015]

By choosing a combination of these amines with an optically active O-alkylpantolactone [1] such as O-methylpantolactone, O-ethylpantolactone, O-*n*-propylpantolactone, or O-benzyl-

pantolactone, the optical resolution can be carried out more efficiently.

[0016]

Effects of the invention

This invention can provide novel optically active O-alkylpantolactones as good optical resolving agents for the production of optically active amines.

[0017]

Practical examples

Practical Example 1

5.0 g of (-)-pantolactone ($[\alpha]_D -50.7^\circ$ (21°C, c 2, water)) was dissolved in 25 mL of N,N-dimethylformamide (hereinafter abbreviated DMF). 8.9 g of silver oxide and 27.3 g of methyl iodide were added and reacted with stirring at room temperature for 1 hr. 100 mL of ether was added, and then the insolubles were removed by filtration. The filtrate was washed with water, dried over anhydrous magnesium sulfate, concentrated, and distilled under reduced pressure to obtain 4.69 g of (+)-O-methylpantolactone. bp 53-55°C/3 torr. $[\alpha]_D +49.2^\circ$ (21°C, c 2, MeOH)

[0018]

Practical Example 2

6.58 g of ethyl iodide was used instead of the methyl iodide of Practical Example 1, and the reaction was carried out with stirring at room temperature for 16 hr. By post-treatment, purification by silica gel column chromatography, and distillation under reduced pressure, 5.27 g of (+)-O-ethylpantolactone was obtained. bp 60-62°C/3 torr. $[\alpha]_D +51.6^\circ$ (21°C, c 2, MeOH)

[0019]

Practical Example 3

3.45 g of (+)-O-*n*-propylpantolactone was obtained as in Practical Example 2 except for using 8.90 g of *n*-propyl iodide instead of the ethyl iodide used in Practical Example 2. bp 71-72°C/5 torr. $[\alpha]_D +48.9^\circ$ (21°C, c 2, MeOH)

[0020]

Practical Example 4

7.30 g of (+)-O-benzylpantolactone was obtained by reacting, post-treating, and purifying by column chromatography as in Practical Example 2 except for using 32.8 g of benzyl bromide instead of the ethyl iodide used in Practical Example 2. This was recrystallized with ethyl acetate

and *n*-hexane. mp 42-43°C. $[\alpha]_D +89.9^\circ$ (21°C, c 2, MeOH)

[0021]

Practical Example 5

5.0 g of (+)-pantolactone ($[\alpha]_D +50.3^\circ$ (21°C, c 2, water) was dissolved in 25 mL of DMF. 8.8 g of barium oxide and 27.3 g of methyl iodide were added, and this was heated and stirred for 2 hr under boiling with reflux. Water was added, and this was extracted with methylene chloride, washed with aqueous NaCl solution, dried over anhydrous magnesium sulfate, and concentrated. After purification by silica gel column chromatography, distillation under reduced pressure was carried out to obtain 3.54 g of (-)-O-methylpantolactone. bp 53-55°C/3 torr. $[\alpha]_D -45.6^\circ$ (21°C, c 2, MeOH)

[0022]

Practical Example 6

12.5 g of ethyl iodide was used instead of the methyl iodide in Practical Example 5, and a reaction was carried out with stirring at room temperature for 18 hr. Post-treatment and purification were carried out as in Practical Example 5, and 2.05 g of (-)-O-ethylpantolactone was obtained. bp 60-62°C/3 torr. $[\alpha]_D -36.9^\circ$ (21°C, c 2, MeOH)

[0023]

Practical Example 7

7.64 g of (±)-1-phenylethylamine was dissolved in 31.5 mL of 2N hydrochloric acid. 9.08 g of (+)-O-methylpantolactone ($[\alpha]_D +49.2^\circ$) was placed in 35 mL of 2N aqueous caustic soda and dissolved with stirring and then adjusted to pH 8 with 2N hydrochloric acid. The two solutions were combined and concentrated to dryness under reduced pressure. 200 mL of methyl ethyl ketone (hereinafter abbreviated MEK) was added, and this was heated to 50°C and then filtered to remove the insolubles. After concentration to dryness under reduced pressure, 72 mL of methanol and 360 mL of isopropyl ether were added, and the residue was dissolved by heating and then crystallized by cooling to 5°C. 6.73 g of crystals were collected by filtration. These crystals were recrystallized with 13 mL of methanol and 65 mL of isopropyl ether, and 4.94 g of crystals of the (+)-O-methylpantoic acid salt of (+)-1-phenylethylamine was obtained. mp 136.5-138°C. $[\alpha]_D +23.7^\circ$ (21°C, c 2, MeOH). 4.00 g of this salt was decomposed with 2N aqueous caustic soda, extracted with ether, and concentrated to obtain 1.64 g of (+)-1-phenylethylamine.

According to HPLC analysis, the optical purity of the amine was 99.0% ee. Also, hydrochloric acid was added to the aqueous layer at this time to adjust it to pH 1, and this was heated and boiled with reflux for 1 hr. This was extracted with ether two times and concentrated, and 1.92 g of (+)-O-methylpantolactone was recovered.

$[\alpha]_D +54.0^\circ$ (21°C, c 2, MeOH). bp 53~55°C/3 torr. ^1H -NMR (90 MHz, CDCl_3): δ 4.00, 3.88 (each 1H, d, $-\text{CH}_2-\text{O}-\text{C}$ O), 3.64 (3H, s, MeO), 3.59 (1H, s, MeOCH), 1.21, 1.10 (each 3H, s, $\text{Me}_2\text{C}<$). IR (NaCl) ν : 2840, 1785, 1465, 1215, 1160, 1120, 1115, 995 cm^{-1} .

[0024]

Practical Example 8

11.9 g of (\pm)-1-(1-naphthyl)ethylamine and 10.0 g of (+)-O-methylpantolactone ($[\alpha]_D +49.2^\circ$) were placed in 100 mL of water, heated and boiled with reflux for 2.5 hr, and concentrated to dryness. 80 mL of acetone and 40 mL of methanol were added, and the residue was dissolved with heating and then crystallized by cooling to 5°C. 7.91 g of crystals were collected by filtration. These were recrystallized with 54 mL of acetone and 27 mL of methanol, and 4.27 g of crystals of the (+)-O-methylpantoic acid salt of (+)-1-(1-naphthyl)ethylamine were obtained. mp 174-176°C. $[\alpha]_D +22.3^\circ$ (21°C, c 2, MeOH). 4.00 g of this salt was decomposed with 2N aqueous caustic soda, extracted with ether, and concentrated, and 1.91 g of (+)-1-(1-naphthyl)ethylamine was obtained. According to HPLC analysis, it was 96.9% ee. Also, hydrochloric acid was added to the aqueous layer at this time to adjust to pH 1, and this was heated and boiled with reflux for 1 hr. It was extracted with ether two times and concentrated, and 1.87 g of (+)-O-methylpantolactone was recovered. $[\alpha]_D +54.1^\circ$

[0025]

Practical Example 9

10.8 g of (\pm)-1-(1-naphthyl)ethylamine was dissolved in 31.5 mL of 2N hydrochloric acid. 10.0 g of (+)-O-ethylpantolactone ($[\alpha]_D +51.6^\circ$) was placed in 35 mL of 2N aqueous caustic soda, dissolved with stirring, and adjusted to pH 8 with 2N hydrochloric acid. The two solutions were combined and concentrated to dryness under reduced pressure. 200 mL of MEK was added,

and this was heated to 50°C and then filtered to removed the insolubles. After concentration to dryness under reduced pressure, 200 mL of isopropanol was added, and the residue was dissolved with heating and crystallized by cooling to 5°C. 7.23 g of crystals were collected by filtration. These crystals were recrystallized with 170 mL of isopropanol, and 5.39 g of crystals of the (+)-O-ethylpantanoic acid salt of (+)-1-(1-naphthyl)ethylamine were obtained. mp 136.5-138°C. $[\alpha]_D^{25} +23.7^\circ$ (21°C, c 2, MeOH). 4.00 g of this salt was decomposed with 2N aqueous caustic soda, extracted with ether, and concentrated, and 1.88 g of (+)-1-(1-naphthyl)ethylamine was obtained. According to HPLC analysis, it was 98.0% ee. Also, hydrochloric acid was added to the aqueous layer at this time to adjust to pH 1, and this was heated and boiled with reflux for 1 hr, extracted with ether two times, and concentrated, and 1.70 g of (+)-O-ethylpantolactone was recovered.

$[\alpha]_D^{25} +55.0^\circ$ (21°C, c 2, MeOH). bp 60~62°C/3 torr. $^1\text{H-NMR}$ (90 MHz, CDCl₃): δ 4.20~3.50 (2H, m, MeCH₂O), 4.00, 3.90 (each 1H, d, -CH₂-O-CO), 3.68 (1H, s, EtOCH), 1.28 (3H, t, CH₃CH₂O), 1.20, 1.10 (each 3H, s, Me₂C<). IR (NaCl) ν : 2840, 1785, 1465, 1215, 1160, 1120, 1115, 995 cm⁻¹.

[0026]

Practical Example 10

10.4 g of (±)-1-methyl-3-phenylpropylamine was dissolved in 35 mL of 2N hydrochloric acid. 12.0 g of (+)-O-*n*-propylpantolactone ($[\alpha]_D^{25} +48.9^\circ$) was placed in 40 mL of 2N aqueous caustic soda, dissolved with stirring, and adjusted to pH 8 with 2N hydrochloric acid. These two solutions were combined and concentrated to dryness under reduced pressure. 120 mL of MEK was added, and this was heated to 50°C and then filtered to remove the insolubles. The solution was concentrated under reduced pressure to approximately 120 mL, and the concentrate was crystallized by cooling to 5°C. 15.09 g of crystals were collected by filtration. These crystals were recrystallized with 100 mL of MEK, and 6.64 g of crystals of the (+)-O-*n*-propylpantoic acid salt of (+)-1-methyl-3-phenylpropylamine were obtained. mp 140-142°C. $[\alpha]_D^{25} +22.2^\circ$ (21°C, c 1, MeOH). 4.00 g of this salt was decomposed with 2N aqueous caustic soda, extracted with ether, and concentrated, and 1.63 g of (+)-1-methyl-3-phenylpropylamine was obtained. According to HPLC analysis, it was 98.0% ee. Also, hydrochloric acid was added to the aqueous

layer at this time to adjust to pH 1, and then it was heated and boiled with reflux for 1 hr, extracted with ether two times, and concentrated, and 1.87 g of (+)-O-*n*-propylpantolactone was recovered.

[α] D+49.0° (21°C, c 2, MeOH). b.p. 71~72°C/5 torr. ¹H-NMR (90 MHz, CDCl₃): δ 4.10~3.37 (2H, m, EtCH₂O), 4.02, 3.88 (each 1H, d, -CH₂-O-CO), 3.65 (1H, s, PrOCH), 1.66 (2H, q, CH₂CH₂CH₂O), 1.20, 1.10 (each 3H, s, Me₂C<), 0.96 (3H, t, CH₂CH₂CH₂O). IR (NaCl) ν : 2875, 1790, 1465, 1375, 1200, 1120, 1030, 1015, 995 cm⁻¹.

[0027]

Practical Example 11

10.57 g of (±)-1-phenylpropylamine was dissolved in 39 mL of 2N hydrochloric acid. 17.22 g of (+)-O-benzylpantolactone ([α]_D +80.9°) was placed in 43 mL of 2N aqueous caustic soda and adjusted to pH 8 with 2N hydrochloric acid. The two solutions were combined and concentrated to dryness under reduced pressure. 200 mL of MEK was added, and this was heated to 50°C and then filtered to remove the insolubles. After concentration to dryness under reduced pressure, this was again dissolved with 70 mL of MEK while heating. The solution was crystallized by cooling to 5°C. 14.19 g of crystals were collected by filtration. These crystals were recrystallized with 160 mL of MEK, and 9.96 g of crystals of the (+)-O-benzylpantoic acid salt of (+)-1-phenylpropylamine were obtained. mp 122-123°C. [α]_D +36.4° (21°C, c 1, MeOH). 8.00 g of this salt was decomposed with 1N hydrochloric acid and adjusted to pH 1, then heated and boiled with reflux for 1 hr, extracted with ether two times, and concentrated, and 4.49 g of (+)-O-benzylpantolactone was recovered. This was recrystallized with a mixed solvent of ethyl acetate and *n*-hexane.

[α] D+91.3° (21°C, c 1, MeOH). mp 42~43°C. ¹H-NMR (90 MHz, CDCl₃): δ 7.37 (5H, bs, C₆H₅), 5.08, 4.73 (each 1H, d, PhCH₂O), 4.02, 3.85 (each 1

H, d, $-\text{CH}_2-\text{O}-\text{CO}$), 3.74 (1H, s, PhCH_2OCH), 1.14, 1.10 (each 3H, s, $\text{Me}_2\text{C}=\text{O}$). IR (NaCl) ν : 1785, 1760, 1120, 985 cm^{-1} .

The aqueous layer was alkalized with caustic alkali, extracted with ether, and concentrated, and (+)-1-phenylpropylamine was obtained. According to HPLC analysis, it was 93.6% ee.

[0028]

Practical Example 12

6.80 g of (\pm)-1-methyl-3-phenylpropylamine was dissolved in 23 mL of 2N hydrochloric acid. 10.00 g of (+)-O-benzylpantolactone ($[\alpha]_D +80.9^\circ$) was placed in 24 mL of 2N aqueous caustic soda and dissolved with stirring, and then adjusted to pH 8 with 2N hydrochloric acid. The two solutions were combined, heated and stirred at 50°C for 30 min, and then crystallized by cooling at 5°C. 14.98 g of crystals (wet) were collected by filtration. These were recrystallized with a mixed solvent of 12 mL of methanol and 36 mL of water, and 6.06 g of crystals of the (+)-O-benzylpantoic acid salt of (+)-1-methyl-3-phenylpropylamine were obtained. mp 147-149°C. $[\alpha]_D +45.4^\circ$ (21°C, c 1, MeOH). 4.00 g of this salt was decomposed with 1 N hydrochloric acid and adjusted to pH 1, then heated and boiled with reflux for 1 hr, extracted with ether two times, and concentrated, and 2.19 g of (+)-O-benzylpantolactone was recovered. $[\alpha]_D +91.0^\circ$. The aqueous layer was alkalized with caustic alkali, extracted with ether, and concentrated, and 1.49 g of (+)-1-methyl-3-phenylpropylamine was obtained. According to HPLC analysis, the optical purity of the amine was 92.8% ee.

[Translator's note: The corrections listed at the bottom of page 771 and the continuation from the front page on page 772 have been incorporated into the text.]